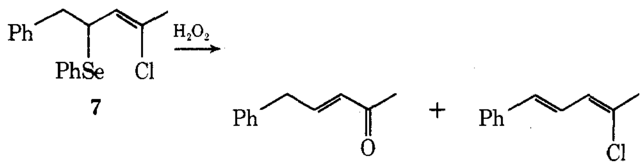

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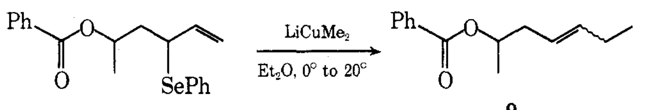

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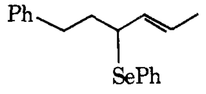

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which methyl has replaced phenylseleno.[19] The transformation of 8 to 9 proceeds with allylic rearrangement giving a mixture of cis and trans isomers. The route from 1 to 8 to 9 results in overall 1,3 disubstitution of an allyl fragment, first by an electrophile, then by a nucleophile. Cinnamyl phenyl selenide gives unrearranged olefin (1-phenyl-1-butene, 65%) upon treatment with dimethylcuprate in ether. Alkylation products of phenyl crotyl selenide (i.e., 10) undergo reaction with dimethylcuprate sluggishly, and the reaction is likely to be limited to the less highly substituted allyl selenides such as 8. Aryl selenides with electron-attracting substituents may undergo more facile displacements by cuprate, and we are exploring this possibility.

Acknowledgment. The donors of the Petroleum Research Foundation, administered by the American Chemical Society, the National Science Foundation, and the Wisconsin Alumni Research Foundation provided generous support for this work.

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(11) Addition of hexamethylphosphoric triamide destroys the α selectivity of chelated sulfur-substituted allyllithium reagents.[3a]

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Received April 18, 1975

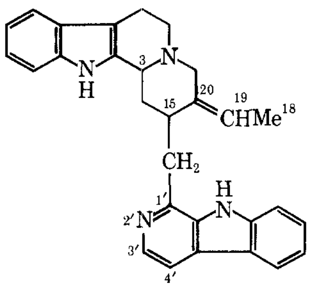
Synthesis and Stereochemistry of (±)-3′,4′-Dihydrousambarensine

Summary: A total synthesis of (±)-3′,4′-dihydrousambarensine has been carried out which confirms the structure and defines the stereochemistry of the alkaloid as **2a**.

Sir: Largely on the basis of spectral data,[1] formulas **1** and **2** were recently suggested for the *Strychnos usambarensis* alkaloids, usambarensine and 3′,4′-dihydrousambarensine. However, no stereostructures have been assigned to these substances, all unusual, indole analogs of the more familiar Ipecacuanha type, which possess isoquinoline rings as the heterocyclic entities. Using totally synthetic starting material of secure stereochemistry, namely, methyl (±)-geissoschizoate (**3a**),[2] we have carried out the first synthesis of 3′,4′-dihydrousambarensine, which not only establishes the gross structure but also defines the geometry and chirality of the natural product as indicated in **2a**.[3]

(±)-Geissoschizoic acid, prepared by saponification of methyl (±)-geissoschizoate (**3a**), was condensed with tryptamine in the presence of dicyclohexylcarbodiimide (dimethoxyethane–dimethylformamide at room temperature) to give tryptamide **4a**. Cyclization of the latter by means of $POCl_3$ in $CHCl_3$ provided, after preparative TLC, (±)-dihydrousambarensine (**2a**), indistinguishable from the natural product on the basis of TLC, uv, ir, and NMR as well as high resolution mass spectral comparisons. That no inversion occurred at the potentially epimerizable center C-3 during the synthesis of (±)-**2a** was substantiated by the result of a parallel series starting with methyl (±)-epigeissoschizoate (**3b**). After successive treatment of this ester with boron tribromide[4] and tryptamine in dichloromethane–benzene, tryptamide **4b** was obtained. On $POCl_3$–$CHCl_3$ cyclization, the amide **4b** generated base **2b**, isomeric with, but different from, natural 3′,4′-dihydrousambarensine, on the basis of TLC and ir spectral properties. In view of the foregoing, the stereochemistry of **3a** corresponds to that of synthetic (±) base **2a**, which accordingly must possess the cis relationship for C-3 and C-15 as well as for the olefinic methyl (C-18) and the C-15 center.

Obviously derived biogenetically from two tryptamine



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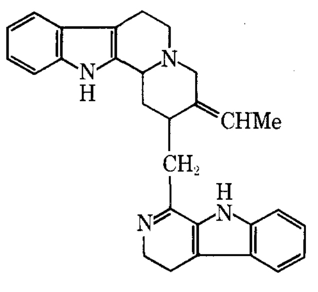

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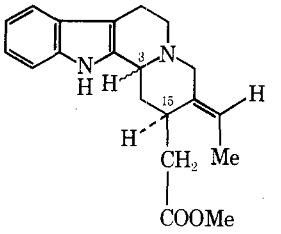
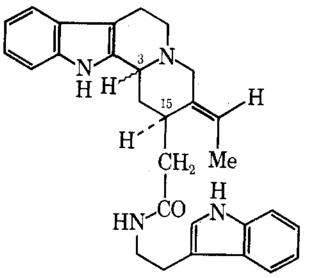
a, 3,15 cis, 18-Me cis to C-15
b, 3,15 trans, 18-Me cis to C-15



3a, 3α-H
b, 3β-H



4a, 3α-H
b, 3β-H

residues and a C_9 terpenoid component, dihydrousambarensine features stereochemical relationships characteristic of (1) terpene-derived indole alkaloids bearing ethylidene groups, normally possessing cis geometry, and (2) the emetine type, having the cis relationship of C-3 and C-15. Further, the oxidation levels of the heterorings in natural products **1**, **2**, and tetrahydro-**2** corresponds exactly to those of the isoquinoline units in emetine, psychotrine, and emetamine.[5] These similarities constitute a remarkable overlap of the various structural features which characterize the two alkaloid classes and suggest action on precursor substrates of very similar—perhaps identical—enzyme species.

Acknowledgment. The authors thank Dr. L. Angenot, University de Liege, for providing a sample of natural dihydrousambarensine, and Professor E. E. van Tamelen, Stanford University, for his kind interest in this work.

Supplementary Material Available. The experimental procedures for the reactions described in this investigation will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $2.50 for photocopy or $4.00 for microfiche, referring to code number JOC-75-2572.

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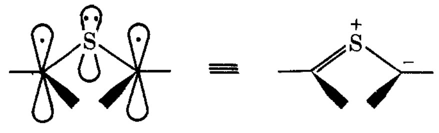
Received March 11, 1975

Thiocarbonyl Ylides.[1] Stereochemical Properties of 4-*tert*-Butylcyclohexyl Derivatives

Summary: The stereoisomeric thiocarbonyl ylides derived formally from 4-*tert*-butylcyclohexanone undergo ring closure in a conrotatory manner providing spirocyclic thiiranes, which may be desulfurized.

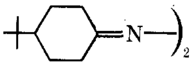
Sir: Thiocarbonyl ylides (1) have revealed their usefulness as tools for theory and as building blocks for synthesis.[2]



1

Methods developed previously by us make now available various aliphatically substituted members of this class of reactive intermediates.[2a] We offer here further insight into the stereochemical properties of thiocarbonyl ylides and in the following articles some applications of the derived products.[3]

Treatment of the azine (**2**) of 4-*tert*-butylcyclohexanone with hydrogen sulfide under pressure gives a mixture of 1,3,4-thiadiazolidines (**3**). Dehydrogenation of this mixture with dimethylazodicarboxylate gives a mixture of **4**, **5**, and **6**.[4,5] The yield is quantitative based on **2**. Separation of **4** and **5** from **6** is achieved by extraction with *n*-pentane in which **6** is totally insoluble. Chromatography over aluminum oxide allows separation of **4** and **5**. The isomers **4–6** were pure as determined by ^1H NMR and ^{13}C NMR spectroscopy[6] and chromatography.[7]



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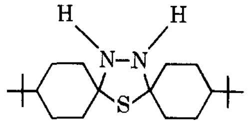
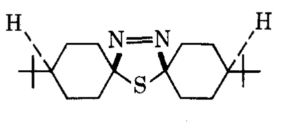
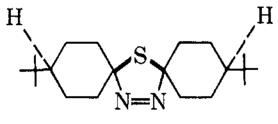


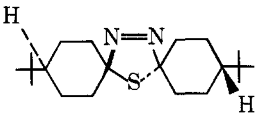
3 (mixture of stereoisomers)



4 (trans,trans), 34%



5 (cis,cis), 23%



6 (cis, trans), 43%

The stereochemistry of **6** was readily ascertained from the observation of two *tert*-butyl absorptions (δ 0.915 and 0.95 in $CDCl_3$) of equivalent intensity in the ^1H NMR spectrum. Moreover in the proton decoupled ^{13}C NMR spectrum eight lines (four pairs) for the ring carbon atoms were noted demonstrating the nonequivalence of the rings. Distinction between **4** and **5** (*tert*-butyl absorptions at δ 0.90 and 0.92, respectively, in $CDCl_3$) was made on the basis of selective shifts observed in the ^1H NMR spectrum induced by $Eu(FOD)_3$. In **5** the axial hydrogens adjacent to the quaternary ring carbon atoms project into the vicinity of the azo bridge, which provides a good complexing site.[8] Absorptions for these protons[9] are shifted strongly downfield on addition of $Eu(FOD)_3$, but in **4** where this steric feature is absent $Eu(FOD)_3$ influences the ^1H NMR spectra only